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Relationship between serum cystatin C level and M694V homozygosity in patients with familial Mediterranean fever

Cystatin C level in patients with familial Mediterranean fever

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Abstract
Aim: In this study we aimed to evaluate the relation of cystatin C with proteinuria, estimated glomerular filtration rate (eGFR), and disease activity in patients with familial Mediterranean fever (FMF).
Material and Methods: One hundred twenty four patients with FMF and 66 healthy controls were included in the study. Complete blood count (CBC), acute phase reactants (erythrocyte sedimentation rate, c-reactive protein), routine biochemical tests, thyroid function tests (TFT), FMF gene analysis, 24-hour urine analysis and serum cystatin C levels were evaluated.
Results: Patients and controls had similar cystatin C levels. A significant negative relationship between creatinine clearance and cystatin C, and a significant positive relationship between microalbuminuria and cystatin C were detected (p=0.008 and p=0.005, respectively) in FMF patients. Cystatin C levels were significantly higher in M694V homozygotes than in M694V mutation-negative patients (p=0.016). Cystatin C levels were higher in men than in women in FMF and control groups (p=0.008, and p=0.003, respectively).
Discussion: In accordance with the literature, creatinine clearance and microalbuminuria were found to be related to serum cystatin C levels. Therefore, cystatin C or cystatin C-based eGFR measurement is important for early detection of nephropathy and early treatment of the disease.

Keywords
FMF; Serum Cystatin C; Proteinuria; GFR

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Introduction

Familial Mediterranean fever (FMF) is the most prevalent hereditary autoinflammatory disease characterized by self-limited recurrent attacks of fever and serositis. It is inherited with an autosomal recessive pattern and affects certain ethnic groups from the Mediterranean basin, mainly Jews, Turks, Arabs and Armenians. The main cause of the disease is mutations in the Mediterranean fever gene (MEFV). This gene encodes pyrin/marenostrin protein. The most common five mutations are M694V, M680I, V726A, E148Q and M694I. Amyloidosis is the most serious complication of FMF and leads to renal failure. M694V homozygous genotype has been associated with a more serious form of the disease, early age of onset, high pleuritis and arthritis risk, and an increased risk of amyloidosis [1-3].

Cystatin C is a cysteine proteinase inhibitor. It can be considered as a new and sensitive parameter than serum creatinine level and creatinine clearance for the monitoring of changes in glomerular filtration rate (GFR) because of being a low molecular weight protein commonly found in the body, its constant endogenous production rate, being freely filtered by the glomerulus, its lacking of tubular secretion and a non-renal excretion pathway and not being affected by the body muscle mass different from creatinine [4]. Another superiority of cystatin C than creatinine is the absence of changes in serum levels depending on gender. However, in the studies including large cohorts of patients, a significant correlation between the degree of inflammation and cystatin C level was detected. Thus, cystatin C has also been proposed as an indicator of not only GFR, but also the degree of inflammation [5,6].

The aim of the present study is to investigate the relationship between serum cystatin C levels and nephropathy development and chronic inflammation in FMF patients, who may develop chronic renal failure due to amyloidosis, for the early determination of renal dysfunction and GFR, and the presence of inflammation.

Material and Methods

One hundred and twenty-four patients fulfilling Livneh criteria [7] with an attack-free period (AFP) and 66 healthy volunteer controls were included in the study. Eighty patients (64.5%) with FMF were female and 44 (35.5%) were male. Among controls, 47 (71.2%) were females and 19 (28.8%) were males. The patients who have thyroid dysfunction, chronic systemic diseases like diabetes mellitus (DM) and/or hypertension or treated with glucocorticoid therapy were excluded from the study. Patients were questioned for age, sex, region of origin, initial symptoms, age at onset of symptoms, age at diagnosis, delay time for diagnosis, family history for FMF, complaints prior to a diagnosis of FMF, response to colchicine treatment, development of amyloidosis and history of appendectomy. The disease severity score was calculated by the scale of Livneh (Table 1) [7]. On admission, white blood cell (WBC), hemoglobin (Hb), platelet, glucose, urea, creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), thyroid stimulating hormone (TSH), fibrinogen, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), 24-hour urine volume and microprotein, creatinine values were measured for each patient and MEFV gene analysis was performed. In the comparisons, M694V mutation was selected because it is the most frequent mutation and related to disease severity. Anemia was defined as an Hb concentration of <12 g/dL in women, <13.5 g/dL in men. Leukocytosis was defined as a WBC count >11000 K/uL. Serum fibrinogen concentrations >400 mg/dL and CRP >5 mg/L were considered high.

Serum was separated from blood samples taken for serum cystatin C and stored at -80°C for about 6 months in a biochemistry laboratory. Serum cystatin C was measured with a turbidimetric method with a Cystatin C-turbilatex® Spinreact kit. The reference range was 0.59 to 1.03 mg/L. The blood tests were taken from patients after fasting for at least 8 hours. In 24-hour urine analysis, proteinuria was defined as protein levels ≥150 mg/day and microalbuminuria was defined as microalbumin levels ≥30 mg/day. Normal healthy volunteers without chronic systemic disease were selected as the control group. Patients and controls were compared in terms of demographic characteristics, disease severity score, laboratory findings and cystatin C levels. Also, patients with FMF were divided into two groups with or without proteinuria and cystatin C levels were compared between two groups.

The study protocol was approved by the local ethics committee and was in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects.

Statistical Analysis

SPSS 17.0 package program was used for the data analysis. Descriptive statistics and continuous variables were shown as mean ± standard deviation or median (minimum and maximum) and categorical variables were also shown as the number of cases and the percentages (%). In comparisons, the Kolmogorov-Smirnov test was used to determine the distribution of all continuous variables and non-parametric statistical methods were used for the variables with skewed distribution. In intergroup comparisons, the Kruskal-Wallis H test for multiple groups, the Mann-Whitney U test for two groups and cross-table statistics for comparison of categorical variables (Chi-squared and Fisher's exact test) were used. For statistical significance, $p<0.05$ was considered significant.

Results

The mean age of 124 patients with FMF included in the study was 36.6±1.27 (34.5, 15-73) years (37.9±1.34 years in women and 34.1±1.12 years in men). The mean age of 66 healthy volunteers in the control group was 37.09±1.29 (35, 16-69) years.

The clinical, laboratory, and demographic findings of the FMF patients were shown in Table 1. The mean age for the start of symptoms was 26.6 ± 13.09 (3-71) years and the mean age of diagnosis was 32.4 ± 13, 16 (9-72) years. The mean delay time in diagnosis was revealed to be 5.6 ± 7.3 (0-36) years. Eighty patients were female (64.5%) and 44 were male (35.5%) and 41.9% of the patients (n= 52) had a family history of FMF. Many of the patients were from Central Anatolia Region (65.3%, n= 81). Twenty-four patients (19.4%) had a history of appendectomy.

The frequencies of symptoms in patients with FMF were 85.4% for abdominal pain, 36.2% for fever, 13.7% for chest pain, 16.1% for arthritis, 11.2% for arthralgia and 0.8% for

Table 1. Clinical, laboratory and demographic findings of FMF patients

	Mean ±standard deviation	Minimum-Maximum
Age of patients (years)	36.6±1.27	15-73
Age of diagnosis (years)	32.4 ± 13, 16	9-72
Delay time in diagnosis (years)	5.6 ± 7.3	0-36
Hemoglobine (gr/dL)	13.7±1.69	7-17.4
WBC (K/uL)	7128±1875	4200-14500
Platelet (K/uL)	235470±68818	125000-546000
Fasting plasma glucose (mg/dL)	86.9±9.85	65-109
AST (U/L)	23.2±11.8	9-120
ALT (U/L)	27.7±20.4	6-144
Urea (mg/dL)	27.2±8.37	9-56
Creatinine (mg/dL)	0.97±0.2	0.5-2.1
Sedimentation (mm/h)	19.6±20.7	1-97
CRP (mg/L)	10.2±1.95	3-137
Fibrinogen (mg/dL)	352±154.8	121-910
TSH (uIU/mL)	1.9±0.96	0.5-4.5
Cystatin C (mg/L)	0.72±0.49	0.12-5.65
Urine volume (mL)	1620±904.6	300-5200
Amount of proteinuria (mg/24h)	375.6±184.7	5-17246
Creatinin clearence (ml/dk/1.73 m^2)	83.2±39.02	3.2-272

Table 2. Comparison of the FMF patients and controls according to their age, urea, creatinin and Cystatin C levels

	Mean age (year)	Urea (mg/dL)	Creatinin (mg/dL)	Cystatin C (mg/(L)
FMF patients	36.6±1.27	27.2±8.7	0.97±0.2	0.72±0.49
M694V homozygotes	35.5±11.7	28.3±6.03	1.05±0.33	1.01±1.1
M694V heterozygotes	34.8±10.6	27.07±7.3	0.97±0.18	0.69±0.25
p-value	> 0.05	> 0.05	> 0.05	0.016*
Controls	37.09±12.9	26.3±7.9	0.93±0.19	0.64±0.13
p-value	0.90	0.42	0.19	0.37

*statistically significant.

Table 3. Disease severity score of the FMF patients [14]

Parameters	Features	Score
Age of onset	<5 years	3
	5-10 years	2
	10-20 years	1
	>20 years	0
Number of attacks (mounth)	>2	3
	1-2	2
	<1	1
Dose of colchicine to control attacks (mg/day)	No response	4
	2 mg/day	3
	1,5 mg/day	2
	1 mg/day	1
Joint involvement	Prolonged arthritis	3
	Acute joint involvement	2
Erysipelas-like erythema	If occured	2
Amyloidosis	If occured	3
	Phenotype 2 FMF	4
Scores	Mild disease	2-5
	Moderate disease	6-10
	Severe disease	>10

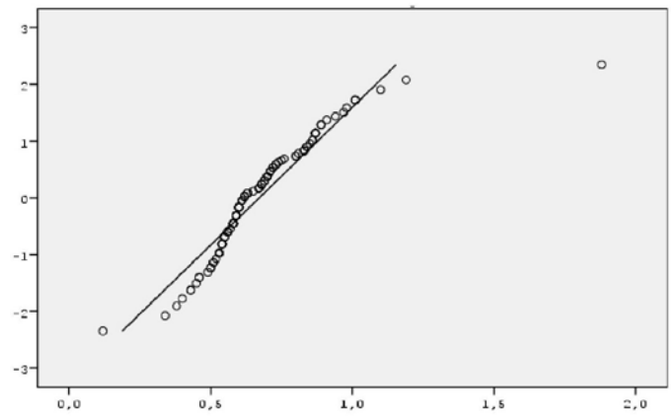

Figure 1. Significant positive correlation between microalbuminuria and cystatin C

erysipelas-like erythema. When the patients with and without arthritis were compared in terms of cystatin C levels, proteinuria and microalbuminuria, there were no statistically significant differences (p=0.15, p=0.62, and p=0.47, respectively).

One hundred and six patients had MEFV mutations; 19 of them had M694V homozygosity, 39 had M694V heterozygosity (single or compound heterozygote with another mutation) and 48 patients had mutations except for M694V. Eighteen patients had no mutation. Cystatin C levels were significantly higher in M694V homozygotes than in M694V heterozygotes and mutation-negative patients (p=0.016) (Table 2).

The mean creatinine clearance of the patients was calculated as 83.2±39.02 (3.2 to 272) mL/dk/1.73 m^2. There was a statistically significant negative correlation between creatinine clearance and cystatin C (p=0.008, r= -0.236). A significant positive correlation between microalbuminuria and cystatin C was also detected (p=0.005, r= 0.618) (Figure 1). In 38 (30.6%) patients, serum CRP and fibrinogen levels were high (>5 mg/L, and >400 mg/dL, respectively). Cystatin C levels were not significantly different in patients with increased or normal CRP and fibrinogen levels and leukocytosis (p>0.05). Proteinuria was detected in 50% of the patients (n=62) and there was no correlation between proteinuria and cystatin C (p=0.49, r= -0.062). While there was not any correlation between ESR and cystatin C, ESR levels were found to be high in patients with proteinuria (p=0.043). In FMF group, cystatin C levels in men were significantly higher than in women (p=0.008).

Of the control group, 47 (71.2%) were female and 19 (28.8%) were male. When the control group was compared with patients with FMF in terms of gender, age and origin, there was no significant difference (p=0.35, p=0.90, p=0.35, respectively). Urea, creatinine, and cystatin C levels were also not statistically different between the two groups (p=0.42, p=0.19, and p=0.37, respectively) (Table 2).

The mean age was 35.6±12.4 years in the male control group and 40.6±13.9 years in the female control group. In the control group, cystatin C levels in men were significantly higher than in women (p=0.003).

Amyloidosis was detected with biopsy in three patients. The levels of cystatin C in patients with amyloidosis were 1,19, 1,01 and 5,65 mg/L, and creatinine levels were 1,5, 1,1 and 2,1 mg/dL. When male and female patients with FMF were

compared for amyloidosis, the presence of proteinuria and the amount of proteinuria, no significant differences were found (p=0.25, p=0.70, p=0.22, respectively), but cystatin C levels in men were significantly higher than in women (p=0.008). When the patients were evaluated according to the disease severity score, 47 (37.9%) patients had mild disease with a score of 2-5, 54 (43.5%) patients had moderate disease with a score of 6-10 and 23 (18.5%) patients had severe disease with a score of ≥10. There was no significant correlation between cystatin C levels and disease severity score (p=0.36) (Table 3).

Discussion

Familial Mediterranean fever is the most common periodic fever syndrome frequently affecting more than 100,000 patients worldwide. The most important complication of FMF is amyloidosis [1]. The delay time in diagnosis was 5.6±7.3 years in our study. This time was found as 6.9 years in the Turkish FMF Study Group's report [8] and 9.3 in the study by Ureten et al [9]. In our study, all three patients with amyloidosis had M694V mutation. While two of them were homozygous for M694V, one of them was compound heterozygous for M694V-M680I mutation.

Among patients with M694V mutation, 32.7% were homozygote and 67.3% were heterozygote (single or compound heterozygote). In the study by Yeşilada et al, M694V mutation rate of FMF patients was found to be 31.7% and similar to our study, 25.5% were M694V homozygote while 74.5% were heterozygote [10]. Guz et al. found that the rate of development of amyloidosis in FMF patients having M694V mutation was 37%, and concluded that this genotype is a risk factor for amyloidosis in FMF patients in Turkey [11]. In genotype-phenotype correlation research on 167 FMF patients, Yalcinkaya et al. found that being carriers of any homozygous or heterozygous mutation does not determine the severity of the disease and the development of amyloidosis in Turks [12]. Similar to this study, we did not find a significant correlation between arthritis and M694V homozygosity. But, we found a significant positive relationship in patients with homozygous M694V mutations and cystatin C levels compared with the patients without M694V mutations. Studies showed the relation between M694V homozygosity and amyloidosis [3]. The relationship between cystatin C and M694V homozygosity has not been studied before. Therefore, our study becomes important in this respect.

In many patients, the inflammation continues during the attack free periods (AFP) that shows higher levels of acute phase proteins, cytokines and inflammation-related proteins [13]. The production rate of cystatin C in inflammatory events does not change [14]. While Evangelopoulos et al. determined a positive correlation between cystatin C and WBC, they did not find a relationship with hs-CRP, haptoglobin, ferritin, and albumin [15]. Grubb et al. investigated the course of acute phase reactants preoperatively and postoperatively for 7 days in 35 patients undergoing elective surgery and they found that there was a significant increase in the levels of serum CRP, serum amyloid-A protein (SAA), haptoglobin and orosomucoid following the operation compared to the preoperative period, but they did not find a significant increase in cystatin C levels in pre- and post-operative period up to 7 days [16]. Similarly, in our study, there was no significant relation between serum CRP, fibrinogen levels, leukocytosis and cystatin C. Recently, in contrast to our study, cystatin C was found significantly correlated with several markers of inflammation in systemic lupus erythematosus patients in the study of Lertnawapan et al. [17].

There are few studies on the relationship between gender and cystatin C. Grubb et al. showed that cystatin C is independent of age and sex [18]. In another study, the elevated levels of cystatin C were independently related to male gender [19]. In our study, in both patient and control groups, when men and women were compared in terms of cystatin C, cystatin C levels were significantly higher in men.

Recently, cystatin C has been proposed as a reliable indicator of GFR compared with creatinine. In the literature, the relationship between cystatin C and FMF has been firstly studied by Deveci et al. They investigated serum cystatin C levels as an early marker of renal involvement in FMF patients. Patients were divided into four groups as attack period, AFP, FMF with amyloidosis, and healthy controls and compared for cystatin C. Eventually, cystatin C was found more effective and accurate than estimated GFR with the cut off level of 876.5 pg/mL [20]. We compared FMF patients and the controls for cystatin C and there was no significant relationship between the two groups. At the same time, there was no correlation between disease activity score and cystatin C. In the literature, according to the results of a study investigating the levels of cystatin C in rheumatoid arthritis, while disease activity was found positively correlated with cystatin C, creatinine clearance was negatively correlated [21]. In the study by Lertnawapan et al, similarly, the levels of cystatin C in patients with rheumatoid arthritis were higher than in controls and were positively correlated with disease activity score [22].

In our study, cystatin C levels were not significantly correlated with arthritis in FMF patients. This outcome was consistent with the fact that the levels of cystatin C does not change in inflammation. In the follow-up of FMF patients, early diagnosis of amyloidosis and the initiation of appropriate early treatment are essential. While there was no significant association between cystatin C and proteinuria, serum cystatin C levels were significantly higher in patients with microalbuminuria. Higher cystatin C levels were detected in patients who had chronic kidney disease with microalbuminuria than those without microalbuminuria by Rifkin et al., and it was shown that each standard deviation increase in cystatin C levels increase the risk of cardiovascular mortality by approximately 20% [23]. However, Jeon et al. found a positive correlation between albuminuria and serum cystatin C levels in type 2 diabetic patients [24]. In contrast to our study, in another research, no correlation between the increase of cystatin C and the urinary albumin was found [25].

This study has some limitations. We could not measure serum cystatin C levels in FMF patients with an attack period. We evaluated the relationship between cystatin C and FMF (in patients with AFP) in this study, and according to our results, the increase in cystatin C levels and the decrease in creatinine clearance are correlated with microalbuminuria. The serum cystatin C measurement for the evaluation of renal involvement in patients with FMF was demonstrated to be a practical, useful,

and noninvasive marker. However, the use of cystatin C as a marker of inflammation is yet limited. Prospective studies with a large number of patients are necessary for certain results.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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